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Meta-Analysis of Intravenous Dipyridamole–Thallium-201 Imaging (1985 to 1994) and Dobutamine Echocardiography (1991 to 1994) for Risk Stratification Before Vascular Surgery

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Objectives. This study evaluated the prognostic value of abnormal test results with pharmacologic stress with regard to perioperative and long-term outcomes in a large population of candidates for vascular surgery.

Background. Although numerous studies have demonstrated the prognostic value of dipyridamole–thallium-201 myocardial perfusion and dobutamine echocardiography in vascular surgery candidates, a synopsis of predictive estimates is difficult because of individual study variability in pretest clinical risk, sample size and study design.

Methods. A systematic review of published reports on preoperative pharmacologic stress risk stratification from the MEDLINE data base (1985 to 1994) identified 10 reports on dipyridamole–thallium-201 myocardial perfusion (1,994 patients) and 5 on dobutamine stress echocardiography (445 patients). Random effects models were used to calculate summary odds ratios and 95% confidence intervals.

Results. Summary odds ratios for death or myocardial infarction and secondary cardiac end points were greater for dobutamine echocardiographic dyssynergy (14- to 27-fold) than for dipyridamole–thallium-201 redistribution (4-fold); wider confidence intervals were noted with dobutamine echocardiography. Pretest coronary disease probability was correlated with the positive predictive value of a reversible thallium-201 defect ($r = 0.70$), increasing sixfold from low to high risk patient subsets. Cardiac event rates were low in patients without a history of coronary artery disease (1% in 176 patients) compared with patients with coronary disease and a normal or fixed-defect pattern (4.8% in 83 patients) and one or more thallium-201 redistribution abnormality (18.6% in 97 patients, $p = 0.0001$).

Conclusions. Meta-analysis of 15 studies demonstrated that the prognostic value of noninvasive stress imaging abnormalities for perioperative ischemic events is comparable between available techniques but that the accuracy varies with coronary artery disease prevalence.

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Angiographically significant and frequently severe coronary artery disease is prevalent among patients with aortic and peripheral atherosclerosis (1–6). This underlying coronary atherosclerotic disease predisposes patients undergoing vascular reconstructive surgical procedures to perioperative cardiac events (1–6). Over the past decade, extensive published reports have evaluated the use of preoperative clinical and noninvasive screening in this population. The ultimate goal of this approach has been to determine high risk subgroups who might benefit from alternative surgical or medical management strategies to improve perioperative outcomes (6).

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Clinical risk factors and the severity of stress-induced noninvasive imaging abnormalities have been correlated with perioperative and late postoperative cardiac events (4,7–12). More recently, ischemic wall motion abnormalities on two-dimensional echocardiography during dobutamine infusion have also been correlated with perioperative cardiac events (13–17). Developing empirically-based evidence from diverse study populations and imaging techniques into a clinical-imaging risk stratification algorithm has been difficult because several studies (10–12,18) have demonstrated a limited predictive value of noninvasive imaging in this setting. To this end, a meta-analysis of the published reports on dipyridamole and dobutamine stress myocardial imaging was performed to develop clinical recommendations for risk stratification of vascular surgical candidates.

Methods

Description of data search. Articles were obtained using the National Library of Medicine MEDLINE data base between 1985 and 1994. From an initial search, a total of 43 articles were obtained under a broad-based search algorithm

Table 1. Study Inclusion and Exclusion Criteria for 15 Published Reports on Preoperative Risk Stratification

Study (ref no.) and Year Published	Institution and Location	Department	Period of Enrollment	Study Design	Blinded Interpretation	Exclusion Criteria	Type of Operation	Study Quality Rating*	Sample Size Sufficient to Detect Difference >14%
Intravenous Dipyridamole Imaging									
Boucher (7)† 1985	Massachusetts General Hospital, Boston, MA	Cardiology	1982–1984	CS	No	UA, high grade ventricular ectopic activity, recent MI, CHF, severe renal disease or COPD	Abdominal aortic or lower extremity vascular surgery	A	No
Eagle (11) 1989	Massachusetts General Hospital, Boston, MA	Cardiology	1984–1987	CS	No	Surgery cancellation or preop CABG	Vascular surgery	A	Yes
Lane (19)‡ 1989	New England Deaconess Hospital, Boston, MA	Cardiology	1984–1987	CS	No	MI <6 mo, COPD, CK >3.0 mg/dl, CHF, UA	Vascular surgery	B	No
Younis (8) 1990	St. Louis Univ. Health Sciences Center, St. Louis, MO	Cardiology	1984–1989	CS	Nuclear	None listed	Lower extremity, AAA, carotid	B	No
McEntroe (20) 1990	New England Medical Center Boston, MA	Surgery	1987–1990	CS	No	None listed	AAA	B	No
Mangano (18) 1991	Univ. of California–San Francisco, San Francisco, CA	Anesthesiology	—	CS	Vascular surgeons	UA, MI or CHF <6 mo, pacemaker or LBBB	Vascular surgery	B	No
Hendel (21) 1992	Univ. of Massachusetts Medical Center, Worcester, MA	Cardiology	1984–1988	CS	Nuclear	UA, emergency procedures	Vascular surgery	B	Yes
Krenowik (12) 1993	Univ. of Iowa Hospitals and Clinics, Iowa City, IA	Surgery	<1990	CS	—	UA, recent catheterization or CABG <12 mo	Aortic or infrainguinal reconstruction, carotid endarterectomy	B	No
Baron 1994 (10)	Hopital Lariboisere, Paris, France	Anesthesiology	3 yr	CS	Nuclear	Preop coronary arteriography and revascularization, recent MI, disabling or persistent angina	AAA reconstruction	A	Yes
Bry 1994 (9)	New England Medical Center, Boston, MA	Surgery	1987–1992	CS	—	None listed	Aortic disease, infrainguinal revascularization	A	Yes
Dobutamine Echocardiography									
Lalka (13) 1992	Indiana Univ., Indianapolis, IN	Surgery	1988–1991	CS	Echo	MI <12 wk, known cardiomyopathy, UA, ventricular arrhythmia	Aortic revascularization	B	No
Langan (14; 1993	Geisinger Clinic, Danville, PA	Surgery	1992	CS	—	None listed	Infrarenal aortic surgery	B	No
Eichelberger (15) 1993	Univ. of Rochester, Rochester, NY	Cardiology	1991–1992	CS	Echo	None listed	Vascular surgery	A/B	No
Poldermans (16) 1993	Thoraxcenter, Rotterdam, The Netherlands	Surgery	1991–1992	CS	Echo	None listed	Vascular surgery	A/B	No
Davila-Roman (17) 1993	Washington Univ., St. Louis, MO	Surgery	1990–1991	CS	—	Inconclusive test results	Aortic or peripheral vascular surgery	A/B	No

*See text (Quality assessment criteria). †Included nonemergent vascular surgery candidates with stable coronary artery disease (chest pain, abnormal electrocardiographic findings, previous myocardial infarction [MI]). ‡Included nonemergent vascular surgery candidates with diabetes. AAA = abdominal aortic aneurysm; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; CK = creatine kinase; COPD = chronic obstructive pulmonary disease; CS = consecutive series; Echo = echocardiographer; preop = preoperative; ref = reference; Univ. = university; UA = unstable angina; — = information not available.

Table 2. Preoperative Patient Characteristics in 15 Published Reports on Preoperative Risk Stratification

Study (ref no.)	No. of Pts	Mean Age (yr)	Men	Typical Angina	CHF	History of MI	History of CAD	1-Vessel Disease	DM	Prior Revasc	BBB on ECG	Q Waves	Abl LV Function
Dipyridamole Thallium-201 Myocardial Perfusion Imaging													
Boucher 1985 (7)	54	63	87.5%	65.0%	0.0%	58.3%	*	11.1%	*	*	*	*	*
Eagle 1989 (11)	254	66	70.5%	29.0%	9.5%	23.0%	*	*	18.0%	8.0%	*	19.5%	*
Lane 1989 (19)	101	65	65.0%	46.0%	26.0%	39.0%	*	*	100.0%	*	*	36.0%	*
Younis 1990 (8)	130	65	72.0%	23.0%	*	20.0%	*	36.9%	30.0%	11.0%	*	*	*
McEnroe 1990 (20)	95	69	57.9%	17.9%	*	28.4%	*	*	*	8.4%	*	*	*
Mangano 1991 (18)	60	*	98.3%	45.0%	18.3%	40.0%	*	*	25.0%	*	0.0%	*	*
Hendel 1992 (21)	360	67	64.7%	25.6%	10.8%	38.1%	38.1%	*	23.1%	17.2%	*	27.2%	*
Kresowik 1993 (12)	190	68	*	*	*	*	41.1%	12.6%	26.0%	*	*	*	6.3%
Baron 1994 (10)	513	63	*	19.0%	2.8%	16.0%	35.7%	*	8.8%	3.7%	*	*	16.4%
Bry 1994 (9)	237	66	69.2%	18.0%	11.0%	30.0%	*	*	34.0%	*	*	29.0%	*
Total	1,994												
Mean	199	66	73.1%	32.1%	11.2%	32.5%	38.3%	20.2%	33.1%	9.7%	0.0%	27.9%	11.4%
Dobutamine Echocardiography													
Lalka 1992 (13)	60	64	78.3%	30.0%	8.0%	33.0%	*	*	18.0%	8.0%	*	*	*
Davila-Roman 1993 (17)	93	67	67.7%	*	6.5%	*	63.4%	*	19.4%	*	*	*	*
Eichelberger 1993 (15)	75	69	60.0%	*	*	37.3%	*	*	26.7%	26.7%	*	*	*
Langan 1993 (14)	81	69	84.0%	23.0%	5.0%	31.0%	*	*	10.9%	27.5%	*	28.0%	13.6%
Poldermans 1993 (16)	136	68	85.3%	17.6%	*	36.0%	41.2%	*	11.0%	*	*	*	12.5%
Total	445												
Mean	89	67	75.1%	23.5%	6.5%	34.3%	52.3%	*	17.0%	20.7%	*	28.0%	13.0%

*Information not available. Abnl = abnormal; BBB = bundle branch block; CAD = coronary artery disease; DM = diabetes mellitus; ECG = electrocardiogram; LV = left ventricular; Pts = patients; Revasc = revascularization; other abbreviations as in Table 1.

using the subject headings *radionuclide imaging, dipyridamole, preoperative and coronary artery disease.* A total of 10 articles were retained for final review (7–12,18–21). A second search included articles published from 1990 to 1994 on linked subject headings: *dobutamine, echocardiography and preoperative.* A total of 5 articles on dobutamine echocardiography were identified, excluding one duplicate patient series (13–17).

Study selection. Inclusion criteria were 1) English language; 2) peer-reviewed articles published between 1985 and 1994; 3) only updated patient populations, defined as the latter of two publications from the same population; and 4) available cardiac event rates classified by noninvasive test results. Studies reporting major general nonvascular surgery results were excluded (22–26). Study end points (cardiac death, myocardial infarction, recurrent ischemia, congestive heart failure) were carefully scrutinized.

Quality assessment criteria. A previously validated study quality grade was assigned to each report by an investigator and independently reviewed at two separate times (27–29). Each report was reviewed for patient inclusion and exclusion criteria, intervention or treatment strategies used, study design and clinical and noninvasive data collected. Quality assessment criteria included (24,25) A) studies with broad generalizability (adequate sample size, sufficient end point definition and ascertainment) to a variety of patients, without significant flaws in research methods (explicit research design, study inclusion and exclusion criteria; multivariable adjustment or covariate stratification); B) studies with a narrower spectrum of generalizability and with only a few flaws that are well described such that their impact on conclusions can be assessed (borderline sample size, sufficient end point definition and ascertainment; study design and methods include limited patient selection criteria, univariable statistics or missing key covariate adjustment); C) studies with several flaws in research methods (small sample sizes or incomplete reporting of study design or methods); and D) studies with multiple flaws in research methods or reports of unsubstantiated opinion (case series containing ≤10 patients). Only studies graded A or B were included in the subsequent analyses.

Evidence tables. Abstracted data were compiled in the form of standard evidence tables, detailing study design, clinical and test characteristics and study end points. An abnormal stress scan response was defined as one or more fixed or reversible thallium-201 myocardial perfusion defects. An abnormal response to dobutamine was defined as new or worsening ventricular wall motion.

Statistics. The estimated odds ratio (95% confidence interval) was based on a random effects model and calculated using FAST*PRO software (30–32). Initial comparisons made regarding the unblinding of imaging test results revealed no differences in predictive estimates from blinded to unblinded patient series (Table 1). Goodness of fit correlation coefficients were calculated for changes in positive predictive value subclassified by the pretest probability of coronary artery disease.

Table 3. Overall Cardiac Complication Rates by Results of Myocardial Perfusion Imaging

Study (ref no.)	No. of Pts	Revascularization					Complications				
		Operation Canceled	Preop Cath	Preop	Postop	Swan-Ganz Use	Cardiac Event	CV Death	Nonfatal MI	Myocardial Ischemia	CHF
Boucher 1985 (7)	54	*	11.1%	8.3%	8.3%	58.3%	16.7%	2.1%	4.2%	10.4%	*
Eagle 1989 (11)	254	11.8%	2.8%	1.6%	*	*	11.8%	2.4%	3.5%	7.5%	3.54%
Lane 1989 (19)	101	0.0%	*	*	*	44.6%	11.0%	3.0%	5.9%	3.0%	4.95%
Younis 1990 (8)	130	6.1%	36.6%	3.6%	1.8%	*	7.2%	3.6%	3.6%	*	*
McEnroe 1990 (20)	95	0.0%	29.5%	8.4%	*	*	9.5%	2.1%	1.1%	6.3%	*
Mangano 1991 (18)	60	*	*	*	*	*	21.7%	1.7%	3.3%	8.3%	8.33%
Hendel 1992 (21)	360	9.2%	*	*	*	*	8.6%	2.1%	6.7%	*	*
Kresowik 1993 (12)†	190	10.5%	37.4%	7.4%	0.5%	*	2.6%	0.5%	2.1%	*	*
Baron 1994 (10)†	513	7.2%	7.2%	2.4%	*	*	18.8%	4.4%	4.8%	13.3%	4.4%
Bry 1994 (9)†	237	*	13.5%	3.8%	*	*	7.2%	1.3%	5.9%	*	*
Total	1,994										
Mean	199	6.4%	19.7%	5.1%	3.6%	51.4%	11.5%	2.3%	4.1%	8.1%	5.3%

*Information not available. †Series used single-photon emission tomographic computed imaging. Cath = catheterization; CV = cardiovascular; Postop = postoperative; other abbreviations as in Tables 1 and 2.

Sample size estimates were based on a comparison of two proportions with a one-sided Fisher exact test (33), which yielded a necessary and sufficient sample size of 191 patients at alpha 0.01 and beta 0.05. A backward stepwise logistic regression was performed on five dipyridamole–thallium-201 reports (7–12) that included clinical history (congestive heart failure, diabetes, angina, history of myocardial infarction, advanced age and male gender) and noninvasive test results (fixed or reversible thallium-201 defect).

Results

Intravenous Dipyridamole–Thallium-201 Myocardial Perfusion Imaging

Clinical and study characteristics. Results from a total of 1,994 vascular surgery candidates were reported in 10 qualifying reports (Table 1). Only 4 of the 10 studies utilized some form of blinded test interpretation. Patients with congestive heart failure were excluded in three studies (7,18,19), patients with severe or persistent angina in one (10) and those undergoing preoperative myocardial revascularization in three (10–12).

Patients were on average 66 ± 9 years old, with a high pretest likelihood of prior coronary artery disease (37.2%) on the basis of a history of a prior myocardial infarction (32.5%), congestive heart failure (11.2%) or typical angina pectoris (32.1%) before vascular surgery (Table 2). Seventy-three percent of patients were men.

Preoperative treatment alterations and postoperative cardiac events (Tables 3 and 4). Vascular surgery was canceled in 6% of patients, primarily because of high clinical risk or noninvasive test results. Twenty percent of patients underwent preoperative coronary arteriography after documentation of one or more reversible perfusion defects, and 5% and 4% of patients underwent preoperative and postoperative myocardial revascularization, respectively.

Postoperative cardiac events included secondary or "soft" end points, defined as unstable angina, ischemic ST-T wave changes or congestive heart failure (Tables 3 and 4). Any such adverse event occurred in 12% of patients (range 7.2% to 21.7%). Rates of cardiac death or nonfatal myocardial infarction were 2% and 4%, respectively.

Dipyridamole–thallium-201 scan results were normal in 730 patients (36%). Fixed perfusion defects were seen in 471 patients (24%), and 793 (40%) had one or more reversible defect. Cardiac event rates were 3%, 11% and 18% (chi-square 51.7, $p = 0.0001$), and cardiac death or myocardial infarction rates were 1%, 7% and 9% (chi-square 25.2, $p = 0.0001$), for normal results, fixed defects and reversible defects on thallium-201 scans, respectively. Dipyridamole-induced ECG ST segment depression occurred in 7% of patients in four studies and was associated with overall and cardiac death or myocardial infarction rates of 27% and 14% (chi-square for any cardiac event 32.8, $p = 0.0001$; chi-square for death or myocardial infarction 8.6, $p = 0.003$). Summary odds ratios for prediction of cardiac events by thallium-201 imaging results (Fig. 1) were 3.5 (95% confidence interval [CI] 2.5 to 4.8) for any ischemic event and 3.9 (95% CI 2.5 to 5.6) for cardiac death or myocardial infarction. Heterogeneity statistics were nonsignificant, indicating homogeneity of the pooled data.

Semiquantitative thallium-201 imaging analysis. When the cardiac event rate was evaluated by semiquantitative thallium-201 results derived from three reports (9,19,20), there was a higher cardiac event rate in patients with two or more (29.6%, 71 patients) than those with one or more (14.4%, 215 patients) reversible defects (chi-square 43.0, $p = 0.0001$).

Long-term cardiac event rates. Long-term cardiac event rates derived in two studies (24,32) were 6.0% in 166 patients

Table 3. *continued*

Myocardial Perfusion Imaging Results											
Normal			Fixed Defect			Reversible Defect			ST Segment Depression		
No. of Pts	Overall Cardiac Events	Cardiac Death or MI	No. of Pts	Overall Cardiac Events	Cardiac Death or MI	No. of Pts	Overall Cardiac Events	Cardiac Death or MI	No. of Pts	Overall Cardiac Events	Cardiac Death or MI
20	0.0%	0.0%	12	0.0%	0.0%	16	50.0%	18.8%	5	40.0%	20.0%
105	4.8%	1.9%	67	20.9%	11.9%	82	30.5%	12.4%	45	35.6%	20.0%
20	5.0%	0.0%	10	0.0%	0.0%	71	14.1%	12.7%	•	•	•
51	0.0%	0.0%	20	10.0%	10.0%	40	15.0%	15.0%	12	8.3%	8.3%
46	4.3%	4.3%	15	46.7%	26.7%	34	26.5%	8.8%	•	•	•
20	15.0%	5.0%	18	22.2%	5.6%	22	27.3%	4.5%	•	•	•
103	1.0%	1.0%	167	11.7%	11.7%	171	14.4%	14.4%	•	•	•
65	1.5%	1.5%	38	2.6%	2.6%	87	3.4%	3.4%	•	•	•
203	15.8%	7.4%	94	24.5%	12.8%	160	19.4%	8.8%	71	25.4%	8.5%
97	0.0%	0.0%	30	16.7%	16.7%	110	10.9%	10.9%	•	•	•
430			347			523			133		
43	32.%	1.4%	35	11.4%	6.8%	52	18.1%	9.0%	13	8.4%	4.8%

with normal thallium-201 scan results. One- to 3-year cardiac event rates (including early perioperative events) were 34.8% and 32.8%, respectively, in 203 patients with fixed and 220 with reversible thallium-201 defects (chi-square 50.6, p = 0.0001). After early perioperative cardiac events were excluded, later event rates in patients with a fixed defect were 1.4 times greater than in those with ≥1 reversible thallium-201 defect (22.7% vs. 16.4%, chi-square 23.7, p = 0.0001).

Effect of preoperative revascularization. Figure 2 illustrates cardiac event rates classified according to the results of dipyridamole–thallium-201 scintigraphy for the 1,994 patients evaluated in these studies. Of 57 patients who underwent preoperative myocardial revascularization, only 3 (6%) had a perioperative cardiac event, whereas of 523 patients who did not undergo coronary revascularization after detection of a reversible defect, 95 (18%) had an event (chi-square 5.5, p = 0.02). Overall cardiac event rates were 3.2% and 11.4% in 430 and 347 patients with normal scan results and fixed-only perfusion defects, respectively (7,9,11,12,32).

Pretest probability of events. Pretest probability of cardiac events was calculated based on previously documented angiographic or symptomatic clinical history of coronary disease (Fig. 3). Population pretest probability differences correlated with the positive predictive value of a reversible defect (r = 0.70). The positive predictive value of an abnormal test result increased 6.0 times between the patients with the lowest to highest pretest probability of coronary artery disease.

From a compilation of 176 patients from two series (11,12), a negative clinical history for signs and symptoms of coronary artery disease was associated with low event rates, averaging 1.1%. For 83 patients with a positive clinical history for coronary artery disease, the cardiac event rate increased from 4.8% for patients with normal results or a fixed defect to 15.6% for 97 patients with a thallium-201 redistribution abnormality (chi-square 30.7, p = 0.0001).

Meta-regression of clinical and imaging covariables. Five trials provided event rates for various clinical and test result descriptors (i.e., percent of elderly; patients with a history of myocardial infarction, typical angina pectoris or diabetes; or ECG abnormalities) (Table 2). These trials were organized such that stepwise univariate and multivariate logistic regression analyses of pooled data could be performed (7–11). High risk clinical predictors (all p < 0.001) identified from these five reports included male gender (67 [15.2%] of 441 patients), angina pectoris (65 [26.6%] of 244 patients), history of myocardial infarction (54 [22.0%] of 245 patients), congestive heart failure symptoms (11 [33.0%] of 33 patients), diabetes (32 [16.8%] of 190 patients) and advanced age (≥65 to 70 years, 67 [24.6%] of 272 patients). The risk of ischemic event classified by clinical history was lowest in male patients (odds ratio [OR] 0.78, p = 0.03) and was greatest in the elderly (OR 2.5, p = 0.0001). For patients with a fixed thallium-201 myocardial perfusion defect, the odds ratio of a cardiac event was 1.8 (p = 0.004) and increased 3.2-fold for patients with a reversible thallium-201 myocardial perfusion defect (p = 0.0001).

Multivariable stepwise logistic regression analysis (Table 5). The single greatest independent predictor of a perioperative cardiac death or myocardial infarction was the presence of a reversible myocardial perfusion defect (p = 0.0001, OR 2.9). This was followed by signs and symptoms of congestive heart failure (p = 0.0001, OR 3.6) and a fixed thallium-201 defect (p = 0.0001, OR 2.7). A patient's risk of a perioperative cardiac event may be estimated by adding up the scores in the last column of Table 5.

Dobutamine Echocardiography

Mean sample size (Table 2) was smaller for dobutamine echocardiographic studies than with dipyridamole thallium-201 imaging reports (89 vs. 199). Of patients undergoing

Table 4. Overall Cardiac Complication Rates by Echocardiographic Results

Study (ref no.)	No. of Pts	Revascularization: Operation Canceled	Revascularization: Preop Cath	Revascularization: Preop	Revascularization: Postop	Swan-Ganz Use	Complications: Cardiac Event	Complications: CV Death	Complications: Nonfatal MI	Complications: Myocardial Ischemia	Complications: CHF	No Dysynergy: No. of Pts	No Dysynergy: Overall Cardiac Events	No Dysynergy: Cardiac Death or MI	New Dysynergy: No. of Pts	New Dysynergy: Overall Cardiac Events	New Dysynergy: Cardiac Death or MI
Lalka 1992 (15)	60	*	6.7%	6.7%	*	*	25.0%	5.0%	10.0%	5.0%	*	22	4.6%	4.6%	38	29.0%	23.7%
Eichelberger 1993 (15)	75	0.0%	*	*	*	*	6.7%	0.0%	2.7%	4.0%	*	48	0.0%	0.0%	27	19.0%	7.0%
Lorgan 1993 (14)	81	6.2%	19.8%	4.9%	*	*	4.1%	0.0%	4.1%	*	*	31	0.0%	0.0%	50	6.0%	6.0%
Poldermans 1993 (16)	125	*	9.9%	0.0%	*	0.7%	11.2%	3.7%	0.0%	6.7%	0.7%	99	0.0%	0.0%	35	42.9%	14.3%
Davila-Roman 1993 (17)	93	2.2%	20.4%	14.0%	*	*	4.5%	1.1%	2.2%	1.1%	1.1%	70	0.0%	0.0%	23	20.0%	4.0%
Total	445											270			173		
Mean	89	2.8%	11.7%	5.4%	*	0.7%	8.1%	2.0%	1.8%	4.2%	0.9%	54	0.4%	0.37%	35	23.4%	11.0%

*Information not available. Abbreviations as in Tables 1 and 3.

dobutamine echocardiography (Table 2), a lower frequency of typical angina (24%), congestive heart failure (6.5%) and diabetes (17.0%) was reported than for patients undergoing dipyridamole–thallium-201.

Predictive value of ischemic test results. A total of 36 cardiac events were reported in 445 patients, of which 17 (47%) were cardiac death or nonfatal myocardial infarction. Per study, cardiac event rates ranged from 4.1% to 29%. Nearly one-third of patients had a dobutamine-induced ischemic response (range 3% to 50%). As depicted in Figure 1, the univariate odds of any perioperative ischemic event ranged from 7.3 to 128.2-fold greater for patients with an abnormal than normal preoperative dobutamine stress echocardiographic response. By comparison, univariate odds of cardiac death or myocardial infarction ranged from 4.0 to 28.5. Summary odds ratios were 27.4 (95% CI 13.0 to 57.7) for any cardiac event and 14.4-fold (95% CI 5.3 to 39.2) greater for cardiac death or nonfatal myocardial infarction. Tests for homogeneity were nonsignificant for predicting any event (chi-square 6.0, $p = 0.19$) and cardiac death or myocardial infarction (chi-square 2.5, $p = 0.64$).

Figure 2 depicts the frequency of ischemic events by dobutamine stress-induced dyssynergy. Of 173 patients with a dobutamine-induced new or worsening wall motion response, 40 (23.1%) had a perioperative ischemic event compared with 1 (0.37%) of 270 patients with a normal stress echocardiographic response (chi-square 64.9, $p < 0.0001$). The positive predictive value of testing was 0.13 (range 0.07 to 0.21) for cardiac death or myocardial infarction and 0.26 (range 0.17 to 0.43) for any cardiac event. There was a weak relation between pretest probability of coronary artery disease and perioperative outcome ($r = 0.16$) (Fig. 3). The negative predictive value of a normal dobutamine echocardiographic response was 0.99 (range 0.93 to 1.00).

No cardiac events were reported in patients with an abnormal stress echocardiographic response who underwent preoperative revascularization (none of 21 patients), a 13-fold risk reduction (chi-square 7.18, $p = 0.007$). Long-term (1 year) cardiac events were reported in one series (17); the event rate was 2.9% for 69 patients with a normal and 15.0% for 20 with an abnormal stress echocardiographic result (chi-square 5.42, $p = 0.019$).

Noninvasive stress imaging comparisons. Summary odds ratios were greater for dobutamine echocardiography (14 to 27) than for dipyridamole-thallium-201 (3.7 to 4.0); 95% confidence intervals were wider with echocardiography as a result of smaller sample sizes (Fig. 4). The probability of a cardiac event was 0.13 (95% CI 0.07 to 0.19) for dipyridamole-thallium-201 imaging and 0.25 (95% CI 0.16 to 0.33) for dobutamine echocardiography.

Discussion

The current report demonstrates the advantages of a rigorous meta-analysis of nonrandomized trial reports on preoperative risk stratification using two widely used imaging modali-

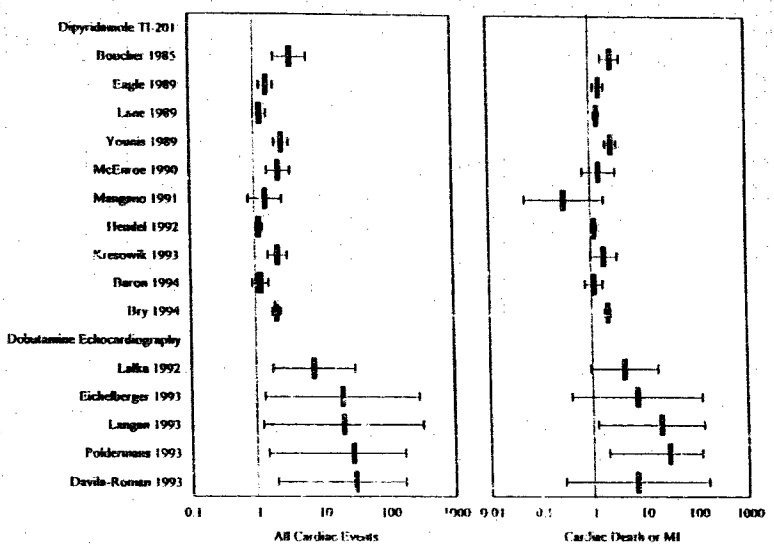

Figure 1. Univariate odds ratio for intravenous dipyridamole–thallium-201 (Tl-201) myocardial perfusion and dobutamine stress echocardiographic imaging for each of the 15 published reports. The odds ratio for any myocardial ischemic event is depicted on the left and that for cardiac death or nonfatal myocardial infarction (MI) on the right. Test for homogeneity: dipyridamole for any event, p = 0.3897; death or myocardial infarction, p = 0.2287; dobutamine for any event, p = 0.19; death or myocardial infarction, p = 0.64.

ties: pharmacologic stress myocardial perfusion scintigraphy and echocardiography. Meta-analysis provides enhanced predictive estimates based on noninvasive test results by reducing variability associated with observational studies of smaller sample sizes. Our results confirm that a reversible perfusion defect or new ventricular dyssynergy during pharmacologic stress is associated with a higher rate of perioperative cardiac death or myocardial infarction. These summary odds data support the current approach of noninvasive assessment of perioperative ischemic risk in vascular surgical candidates. The pretest likelihood of coronary artery disease is the key variable influencing the predictive accuracy of pharmacologic stress imaging for early and late mortality after vascular surgery (3).

Preoperative risk stratification. Studies of consecutive patients undergoing cardiac catheterization before vascular surgery have shown an incidence of angiographically significant coronary artery disease as high as 75% (34,35). Preoperative assessment based on clinical signs and symptoms of coronary

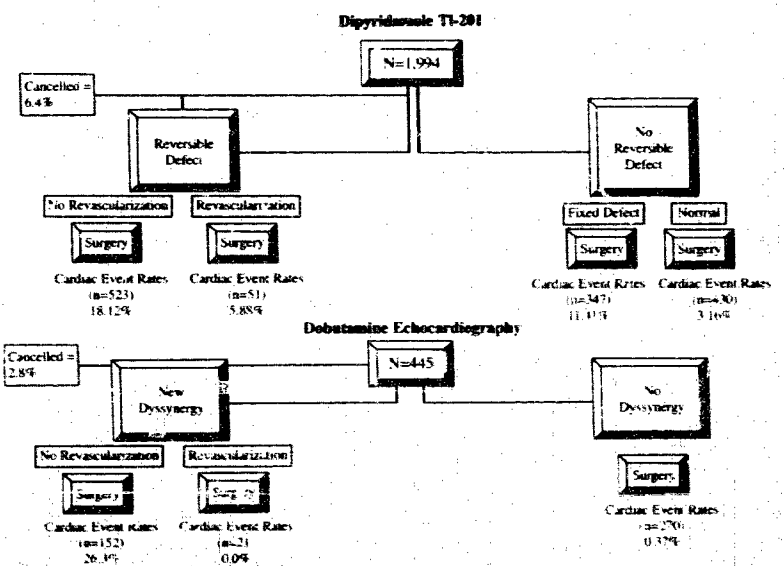

Figure 2. Cardiac event rates after risk stratification by preoperative coronary revascularization and myocardial perfusion results for dipyridamole–thallium-201 (Tl-201) imaging in 1,994 patients. A threefold lessening of risk was observed for patients undergoing preoperative coronary revascularization. Patients with normal thallium-201 scan results had a cardiac event rate of 2%. By comparison, for dobutamine echocardiography (445 patients), cardiac event rates were 0.37% for patients with a normal response versus 26.3% for those with a new wall motion abnormality. No cardiac events were reported in 21 patients undergoing preoperative revascularization after abnormal test results.

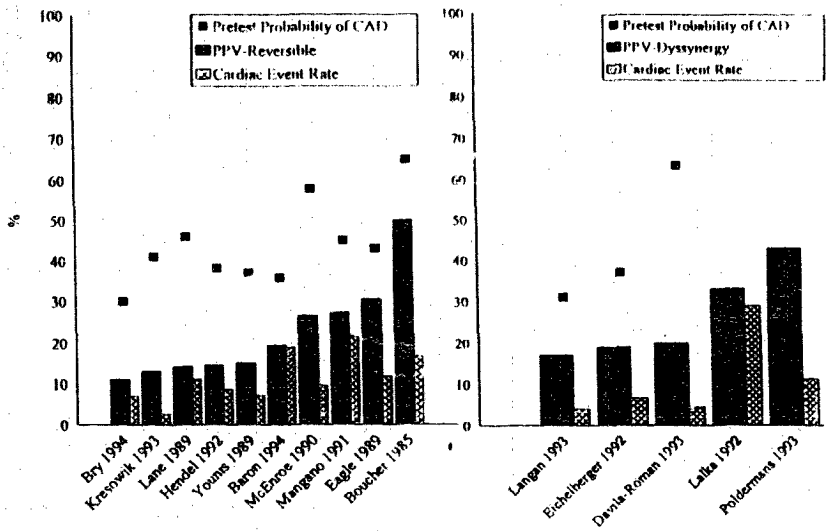

Figure 3. There is a moderately strong ($r = 0.70$) correlation for positive predictive value (PPV) of a reversible defect with the pretest probability of coronary artery disease (CAD) such that the positive predictive value increases 5.93 times between the lowest and highest prior probability of coronary artery disease. By contrast, there is no correlation ($r = -0.16$) between cardiac event rates, pretest probability of coronary artery disease and the positive predictive value of an abnormal dobutamine stress echocardiographic response.

artery disease is difficult as a result of functional impairment and coexisting diabetes (36). Studies attempting to clarify preoperative and postoperative patient management strategies have generally concluded that evidence of ischemic noninvasive imaging is a crucial determinant of future risk. Although some have argued for routine use of coronary arteriography in all high risk patients (12), dipyridamole–thallium-201 scintigraphy, left ventricular ejection fraction and clinical risk factor indices have been widely integrated into preoperative screening algorithms to predict significant coronary artery disease.

Pharmacologic noninvasive imaging has provided clinicians with data on which the decision for further surgical and medical interventions may be based. Despite higher initial imaging costs with pharmacologic stress than with exercise,

Table 5. Logistic Regression Multivariable Model for Predicting Perioperative Cardiac Events (five published reports for a total of 1,188 patients)*

	Step	Total	Cardiac Event Rate	Chi-Square	Beta Coefficient	SE	p Value	Odds Ratio	Relative Contribution	Score
Reversible thallium-201 defect	1	404	22.52%	59.47	1.07	0.14	0.0001	2.93	29.91%	84
Congestive heart failure	2	45	33.0%	28.34	1.27	0.25	0.0001	3.57	14.26%	109
Fixed thallium-201 defect	3	191	21.47%	26.47	0.99	0.19	0.0001	2.69	13.31%	78
Angina pectoris	4	244	26.64%	26.27	0.84	0.16	0.0001	2.32	13.21%	66
ST depression	5	133	27.82%	22.18	0.87	0.18	0.0001	2.38	11.16%	69
Myocardial infarction	6	245	22.04%	20.64	0.73	0.16	0.0001	2.08	10.38%	57
Elderly	7	272	24.63%	10.61	1.01	0.31	0.0011	2.74	5.34%	80
Male gender	8	441	15.19%	4.82	0.33	0.15	0.028	1.39	3.43%	26
Constant					−2.31	0.11				

*Derived from Baron et al. (10), Eagle et al. (11), Younis et al. (8), Bry et al. (9), Boucher et al. (7). Diabetes was omitted from the final backward logistic regression model. To calculate the probability of a perioperative event, add scores for last column for each patient risk marker.

Score	% Risk	Score	% Risk
≤50	5%	151–182	50%
50–70	10%	183–213	60%
70–80	20%	214–249	70%
80–115	30%	250–291	80%
116–150	40%	292–355	90%
		356+	95%

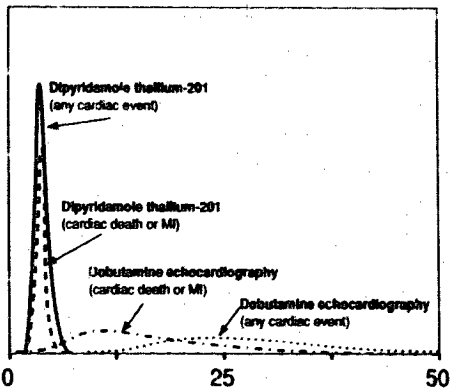

Figure 4. Summary odds ratios and 95% confidence intervals for risk stratification with pharmacologic stress perfusion and echocardiographic imaging as determined by the meta-analytic confidence profile method (providing a probability distribution of point and bound estimates). Because of larger sample sizes, narrower confidence profiles are seen for dipyridamole–thallium-201 myocardial perfusion imaging than for dobutamine stress echocardiography, although the point estimates for summary odds ratios are greater using echocardiography. MI = myocardial infarction.

Shaw and Miller (37), using secondary economic analyses, recently showed that a strategy of preoperative risk stratification with dipyridamole–thallium-201 imaging, in addition to reducing perioperative cardiac deaths (2%), is cost-effective compared with routine use of coronary angiography. A substantial per patient cost savings was accrued, ~80%, when preoperative risk stratification included pharmacologic stress imaging and selective cardiac catheterization was compared with direct catheterization in all vascular surgery candidates.

Predictive value of noninvasive testing. A wide range of predictive accuracies for noninvasive testing was encountered from these diverse studies. To examine the predictive value of noninvasive testing, we collected available clinical history and noninvasive test data from five reports. The results of a multivariable regression model revealed that the presence of a reversible myocardial perfusion defect was the single greatest factor contributing to postoperative cardiac risk. Thirty percent of the cumulative predictive power for adverse cardiac events was contributed by this finding, which was incremental and provided nearly twice the predictive information than the remaining clinical or test variables in the model.

In a large series of catheterized patients (38) the presence of stress-induced wall motion abnormalities provides substantial independent predictive information regarding long-term survival in medically treated patients with coronary artery disease. Similarly, in patients with a high pretest risk of coronary artery disease, the odds of a perioperative cardiac event were elevated sevenfold, and the "hard" event rate increased 14-fold, in patients with dobutamine-induced transient asynergy (39). New or worsening wall motion abnormalities were associated with a high probability of a cardiac event (0.25), although the confidence range for this point estimate was wide because of the low number of patients studied (Fig. 4).

Test results are affected by a variety of technical and patient selection differences. For example, the specificity of echocardiographic wall motion abnormalities is also adversely affected in the presence of an intermediate stenosis (50% to 70%), single-vessel disease as well as submaximal stress (40). Although single-photon emission computed tomographic (SPECT) imaging has been shown to enhance detection of coronary artery disease (41), three of the current reports (9,10,12) document a higher rate of false positive scan results. The trend toward the use of increasingly sensitive but less specific myocardial imaging technology may influence the positive predictive value of preoperative risk stratification findings in future trials.

Influence of pretest likelihood of disease. Selected clinical risk markers that have been correlated with perioperative and postoperative events are widely utilized to triage patients for further testing. These include diabetes, (11,18,21,23) prior myocardial infarction (2,11,19,43–45), abnormal electrocardiographic results (43,44,46,47), congestive heart failure (19,22,43,46,47), advanced age, (11,22,23,46–48) angina (2,8,11,19,46,48), arrhythmias (11,43,44,46,49), prior stroke (43) and hypertension (46). By combining variables, several clinical scoring indexes (4,11,43,44) have been generated using multivariable regression techniques. For example, Eagle et al. (11) identified five clinical variables that were independent predictors of postoperative cardiac events: advanced age (>70 years), ECG Q waves, diabetes mellitus, history of ventricular arrhythmias and history of angina. On the basis of the previous research of Eagle et al., our meta-analysis reports that a combined clinical–imaging preoperative algorithm appears most effective in identifying risk. That is, for patients with one or two clinical risk predictors, the presence of thallium-201 redistribution demonstrated incremental prognostic value. Of patients with coronary artery disease without and with a redistribution perfusion abnormality, cardiac event rates were 11% and 23%, respectively. Importantly, clinically low risk patients have an event rate of 1% regardless of the myocardial imaging results (11,12).

Further, noninvasive test performance is influenced by the pretest disease prevalence and the posttest likelihood of adverse events. The current meta-analysis examined varying predictive models to more fully explore the influence of patient selection differences on the predictive value of this screening approach. Bayesian theory suggests that if the prior probability of disease is low, then screening tests will be of limited value. In one recent series of 1,487 patients (5), perioperative cardiac death or nonfatal myocardial infarction was increased nearly sixfold for patients with compared with those without coronary artery disease.

The combination of clinical history and noninvasive assessment, as based on the present report, enhances preoperative risk assessment. Our results from 10 published reports reveal that the positive predictive value of a reversible thallium-201

myocardial perfusion defect for cardiac events is directly proportional to the prior probability of disease (Fig. 4). The correlation between pretest probability of disease and posttest likelihood of cardiac events was weak for five studies of dobutamine stress echocardiography. The positive predictive value of a reversible thallium-201 defect was nearly six times greater in those studies with the greatest average pretest probability of coronary disease than those with lower pretest disease estimates. In this clinically risk-adjusted analysis, results from dipyridamole perfusion imaging (i.e., ST depression and fixed and reversible defects) contained approximately half the predictive power.

Effect on interventions designed to improve outcomes. Although there is an inherent procedural risk with coronary revascularization, pooled randomized trial data demonstrate that clinically high risk patients derive the greatest survival benefit from coronary bypass surgery than from medical therapy and that this outcome difference persists up to 10 years (50). Several nonrandomized studies (51–53) have suggested that preoperative coronary revascularization may reduce the risk of cardiac death or nonfatal myocardial infarction associated with peripheral vascular surgery by twofold to fourfold. Our synthesis of largely observational data reveals that a strategy of clinical noninvasive risk stratification may be most effective if patients with an intermediate to high likelihood of an adverse event are identified and then undergo intervention to reduce short- and long-term cardiac event risks. Patients with a reversible myocardial perfusion defect undergoing myocardial revascularization had an overall threefold reduction in risk; only 3 of 51 patients undergoing coronary bypass surgery or percutaneous coronary angioplasty experienced a cardiac event (7–11). Preoperative coronary revascularization was equally effective in reducing risk in the reports on dobutamine echocardiography. Elective vascular surgery was canceled in 3% to 6% of all patients because of high risk symptoms or noninvasive test results. It is also possible that a cardiac event was averted in these patients because the results of the screening strategies used led to more aggressive antiischemic medical therapy or coronary revascularization.

Predictive value of noninvasive imaging for late cardiac events. Early studies (7,8,19) using dipyridamole–thallium-201 imaging did not report an increased rate of perioperative events in patients with fixed perfusion defects. The predictive value of a 4-h post-stress fixed defect has increased steadily over the past decade, in part due to emerging data on the potential for severe ischemia in the presence of persistent thallium-201 defects (40). Forty-six percent of all cardiac events occurred in patients with fixed defects in one study (20) and increased the risk of cardiac death fourfold in another (21). Late cardiac event rates were largely comparable in patients with fixed and reversible defects, with approximately one-third of patients with either defect pattern experiencing a cardiac event 2 to 3 years after vascular surgery (8,20,55). Thus, it appears that whereas short-term morbidity and mortality may be much greater in patients with a reversible defect, differences in long-term cardiac event rates are indistinguishable between a fixed or reversible thallium-201 defect. Similar predictive accuracy has been reported for exercise and dobutamine stress echocardiography (40,56). In one dobutamine series (17) that reported 1-year outcome data based on noninvasive imaging results, patients with a normal stress echocardiographic response have a substantially lower cardiac event rate than those with abnormal test results.

Limitations of meta-analysis. Within a meta-analysis (30) bias may arise when publications with more extreme results are selected because they are statistically significant. Precise details of patient management during the intraoperative time period were largely unavailable and may have led to imprecise estimates of the value of preoperative risk stratification strategies. Although we were able to demonstrate that noninvasive risk stratification is valuable in the preoperative setting, a causal link between preoperative ischemia and postoperative complications may not be inferred. Further, duplicate publications from the same patient series would inappropriately weight a meta-analysis and were therefore excluded (7,11,22, 23,25,26,42,57–60). It is reasonable to assume that changes in patient referral patterns and posttest management occurred from 1985 to 1994. A clinical "training effect" may have modified referral based on pretest likelihood of coronary disease and, thus, posttest cardiac event rates and our predictive estimates.

Conclusions. Four key conclusions can be derived from the published data on preoperative stress imaging in vascular surgery candidates: 1) The presence of a reversible dipyridamole–thallium-201 myocardial perfusion defect has positive predictive value, but the accuracy of cardiac event prediction varies with coronary artery disease prevalence and the symptomatic or risk factor profile of the study population. 2) Dobutamine-induced echocardiographic wall motion abnormalities are predictive of adverse perioperative outcomes, but with wider confidence limits due to smaller sample sizes in these studies. 3) The use of varying cutpoints, such as those used in semiquantitative image analysis, may aid in risk identification of clinically lower and higher risk patients. 4) A fixed thallium-201 perfusion defect predicts long-term cardiac events with accuracy equal to the predictive value observed with a reversible thallium-201 defect for perioperative events.

These summary data substantiate the incremental predictive value of noninvasive preoperative risk stratification using pharmacologic stress imaging in vascular surgery candidates while clarifying the influence of patient covariables on test performance characteristics. This analysis supports the use of screening with dobutamine or dipyridamole pharmacologic stress imaging in intermediate risk patients. Although the past decade of experience demonstrates that drug stress imaging is an integral and valuable component of the preoperative patient management strategy, future research on new or existing technologies should be based on large populations to enhance statistical power and to permit the accurate pretest stratification of patients according to their likelihood of significant coronary artery disease and serious cardiac events.

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